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One-pot near-ambient temperature syntheses of aryl(difluoroenol) derivatives from trifluoroethanol†

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Difluoroalkenylzinc reagents prepared from 1-(2'-methoxy-ethoxymethoxy)-2,2,2-trifluoroethane and 1-(*N,N*-diethylcarbamoyloxy)-2,2,2-trifluoroethane at ice bath temperatures underwent Negishi coupling with a range of aryl halides in a convenient one pot procedure. While significant differences between the enol acetal and carbamate reagents were revealed, the Negishi protocol compared very favourably with alternative coupling procedures in terms of overall yields from trifluoroethanol.

Introduction

The major strategic importance of palladium-catalysed coupling reactions within the canon of synthetic organic chemistry was recognised recently by the award of the Nobel Prize for Chemistry to Heck, Negishi and Suzuki. Their methods are now used routinely in academic and industrial facilities for applications ranging from discovery to production chemistry. For high atom efficiency and low environmental impact, few palladium-catalysed coupling procedures can rival the coupling first described by Negishi in 1977.^{1,2} Organozinc species were found to be excellent coupling partners and participated in a wide range of palladium-catalysed aryl–aryl,¹ aryl–alkenyl³ and alkenyl–alkenyl⁴ coupling reactions.⁵ Negishi coupling has also been widely used in natural product synthesis, demonstrated by the groups of Schreiber⁶ and Smith⁷ in their syntheses of discodermolide A. Schreiber performed Negishi coupling with an alkenylzinc reagent while Smith utilised an alkylzinc fragment in an alkyl–alkenyl coupling. Negishi performed no fewer than 6 zinc-based couplings in his synthesis of xerulin⁸ and further demonstrated the usefulness of Negishi coupling in constructing linear unsaturated systems with a short synthesis of β -carotene.⁹ More recently enigmazole A was synthesised using a key oxazolylzinc intermediate in an heteroaryl–alkenyl coupling step.¹⁰

Organozinc species are reactive, yet tolerate many functional groups, including some which bear acidic protons;^{11–13} however,

they were under used until recently due to their reported air and moisture sensitivity.^{14–16} The availability of new and more reliable methods of generating organozinc reagents has rekindled interest in this powerful coupling chemistry, and there have been some spectacular recent results. Knochel and co-workers have previously demonstrated a zincation of aromatic and heteroaromatic compounds bearing sensitive functionalities with 2,2,6,6-tetramethylpiperidide zinc chloride-lithium chloride (TMP-ZnCl-LiCl).¹⁷ More recently this base has been shown to participate in a remarkable zincation of alkenes α - to nitro and cyano functionalities, with the subsequent organometallic species able to undergo Negishi coupling.¹⁸



1, X = F;
2, X = OH;
3a, X = OMEM;
3b, X = ODEC.

4a, X = OMEM;
4b, X = ODEC.

(OMEM = OCH₂O(CH₂)₂OCH₃; ODEC = OCONEt₂)

Palladium-catalysed coupling methods have also been used effectively for the synthesis of selectively fluorinated molecules; the availability of metallated difluoroalkenes from new refrigerants like HFC-134a (**1**), and from other bulk compounds like trifluoroethanol (**2**), has ensured valuable entry points which we and others have used in syntheses of fluorinated analogues of natural products.^{19,20} For example, the dehydrofluorination/metallation reactions of acetal **3a** and carbamate **3b** have been used to prepare stannanes **4a** and **4b**. We deployed **4a** in a synthesis of pentulose analogues²¹ and **4b** in syntheses of difluorinated carbasugar analogues.^{22,23} We were also able to prepare small libraries of compounds structurally related to inhibitors of proteases and other enzymes, using a divergent approach enabled by Stille coupling of **4a** with 4-iodophenyl triflate (Scheme 1).²⁴ Selective coupling set the stage for subsequent Suzuki couplings of **5** with a range of boronic acids (40–84%). Protolysis of the

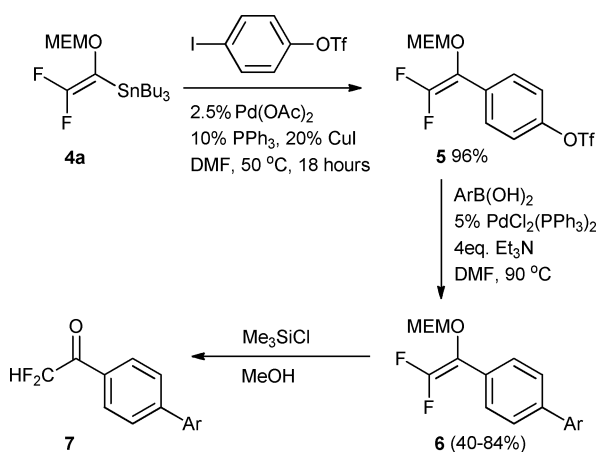
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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and spectra, and Cartesian coordinates and energies. See DOI: 10.1039/c1ob06372c

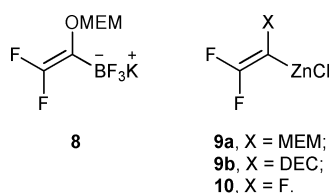
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Scheme 1

difluoroenol acetals **6** completed the sequence, revealing a valuable difluoromethyl ketone motif,^{25–27} small libraries of ketones **7** could be prepared in this way. This reaction also proceeded smoothly with halogen and sulfur electrophiles affording an entry to a range of halodifluoromethyl and (arythio)difluoromethyl ketones.²⁸ This chemistry represents a concise and versatile way of preparing a very wide range of difluoromethyl ketones. Competitive methods, such as Uneyama's reductive defluorination of trifluoromethyl ketones,^{29,30} which can operate close to ambient temperature, have significant advantages over low temperature chemistry, even though each trifluoromethyl ketone must be made separately. Carrying out reactions at low temperature at scale is very expensive; refrigeration plant is costly to buy and run, and special reactors can be required. Solvent viscosity rises at low temperatures and inefficient agitation can lead to poor heat transfer and the development of hot spots in reactions. As there are few methods for the preparation of selectively fluorinated reactions which are practical at scale (because of reagent cost, toxicity or the requirement for low temperature), moving our versatile trifluoroethanol chemistry up from $-78\text{ }^{\circ}\text{C}$ towards ambient would be a promising development.

Recently, a group from Merck showed that the trifluoroborate technology pioneered by Genêt^{31,32} and elaborated by Molander^{33,34} could be adapted for the synthesis of selectively fluorinated molecules from trifluoroethanol *via* Suzuki coupling.^{35,36} Though the synthesis of crystalline borate **8** required a low temperature ($-78\text{ }^{\circ}\text{C}$) reaction, the subsequent chemistry avoided the use of toxic tin reagents. Reagent **8** coupled with a range of aryl bromides in the presence of palladium dichloride pre-catalyst and bulky RuPhos ligand.



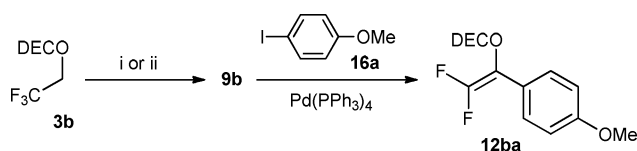
We wished to see if this type of procedure could be used to generate **9a** and **9b** from **3a** and **3b**, and deploy them in coupling reactions. Burton had showed that HFC-134a **1** could be used to begin a Negishi-coupling approach to trifluorostyrenes; the key

alkenylzinc reagent **10** could be generated at $0\text{ }^{\circ}\text{C}$ by exposing **1** to LDA in the presence of zinc chloride.^{37,38}

We also wished to qualitatively evaluate the effects of groups capable of coordinating to zinc, on the outcomes of coupling reactions. Relatively little is known about the identities of the reactive organozinc species which undergo transmetalation to palladium during the catalytic cycle, though important recent discoveries by Lei and co-workers,³⁹ Hevia⁴⁰ and Organ⁴¹ have indicated that a range of organozinc and organozincate species may all play parts in the reaction. In this manuscript, we will describe the development of a near ambient ($0\text{ }^{\circ}\text{C}$) dehydrofluorination/zincation and Negishi coupling protocol, survey its scope and limitations, and compare and contrast its performance with selected Stille and Suzuki couplings. We will also make a preliminary *in silico* exploration of the structures available to the organozinc reagents.

Results and discussion

Acetal **3a**, carbamate **3b** and stannane **4a** were prepared by our published procedures.^{42,43} Borate **8** (55%) was prepared in one pot from **3a** by an adaptation of a procedure of Genêt and co-workers;³² in contrast to the observations of Katz and co-workers, isolation of an intermediary boronic acid or ester was unnecessary.³⁶ Dehydrofluorination/metallation of carbamate **3b** was carried out with *tert*-butyllithium (2 equivalents) in THF at $-78\text{ }^{\circ}\text{C}$ in the first instance. These conditions were chosen to allow the unambiguous preparation of the organolithium reagent.²² A solution of freshly-fused zinc chloride (1.1 equivalents) in THF was added and the mixture was held at $-78\text{ }^{\circ}\text{C}$ for 2 h, then allowed to warm to room temperature ($15\text{--}18\text{ }^{\circ}\text{C}$). After 30 min, the mixture was cannulated onto a mixture of 4-iodoanisole **16a** (1.1 equivalents) and *tetrakis*(triphenylphosphino)palladium(0) (5 mol%), and heated at $65\text{ }^{\circ}\text{C}$ for 16 h. After work-up and purification, we obtained **12ba** as the sole fluorinated product in *ca.* 70% yield (Scheme 2). This result showed that **9b** was both stable at room temperature and available for coupling under palladium-catalysed conditions at higher temperatures. We then implemented a series of step changes by replacing the alkylolithium base with LDA, raising the dehydrofluorination/metallation reaction temperature to $0\text{ }^{\circ}\text{C}$ and having the zinc(II) salt present from the beginning of the sequence, as described by Burton.^{37,38} Freshly-prepared LDA (2.5 equivalents)⁴⁴ was added to a mixture of **3b** and freshly-fused zinc chloride in THF at $0\text{ }^{\circ}\text{C}$. A yellow solution formed immediately and this colour persisted after stirring for 1 h at $0\text{ }^{\circ}\text{C}$ and a further hour at room temperature ($15\text{--}18\text{ }^{\circ}\text{C}$). Reagent **9b** was cannulated onto a mixture of **16a** (1.1 equivalents) and *tetrakis*(triphenylphosphino)palladium(0) (5 mol%), and heated at $65\text{ }^{\circ}\text{C}$ overnight. Once again, we were able to isolate **12ba** in good (65%) yield from **3b**. We were very pleased



i, *t*-BuLi, ZnCl₂, THF, $-78\text{ }^{\circ}\text{C}$ then $15\text{ }^{\circ}\text{C}$; ii, LDA, ZnCl₂, THF, $0\text{ }^{\circ}\text{C}$ then $15\text{ }^{\circ}\text{C}$.

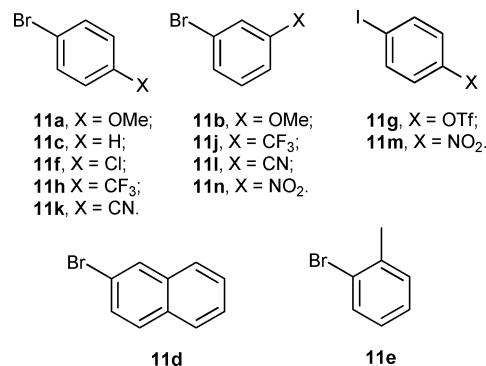
Scheme 2

with this result; while Burton's precedent was a very strong one, the effect of strongly coordinating groups within the alkenylmetal was difficult to predict. Pleasingly, reducing the palladium catalyst loading to 2 mol% did not lower the reaction yield so subsequent reactions were carried out at this loading.

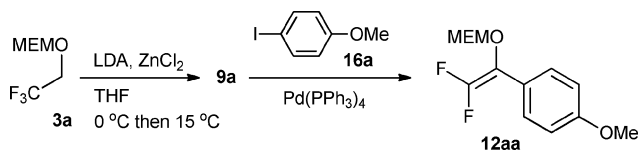
The order of addition of the reactants was investigated briefly, but no advantage accrued from, for example, mixing base and zinc(II) salt before the addition of **3b**. The addition of LDA (2.5 equivalents) to a solution of **3b** and zinc(II) chloride (1.1 equivalents) in THF appeared to be the most straightforward protocol because it minimised the number of reagent transfers. This procedure was applied to the potentially more problematic acetal **3a** (Scheme 3); the (methoxy)ethoxymethyl (MEM) protecting group is cleaved by Zn(II) salts⁴⁵ and so reagent and product stability were uncertain. Low conversions of **3a** were observed under the conditions used for **3b** (as indicated by the ¹⁹F NMR spectra of the crude coupling reaction mixtures). Table 1 summarises initial investigations of the reaction of acetal **3a**. Whereas **3b** was consumed completely after 2 h, **3a** underwent dehydrofluorination/metallation more slowly, with only a moderate conversion (65%) of **3a** after 3.5 h (total reaction time, Table 1, entry 2). These results indicate that **3a** and **3b** undergo dehydrofluorination/metallation at different rates, and that incomplete conversion of the trifluoroethyl starting material leads to a low yield of coupled product. There was little to be gained from increasing the reaction time further (entry 3). The use of 3 equivalents of LDA (entry 4) delivered a disappointing yield of product after isolation (34%) despite high conversion (93%); the ¹⁹F NMR spectrum had a low signal-to-noise ratio, and very broad peaks, strongly suggestive of extensive defluorination. Similar results were observed when LDA was added at room temperature (entry 5). We noted that the reaction was slightly exothermic at room temperature; decomposition may be the consequence of failure to control it. The non-hygroscopic zinc(II) chloride-TMEDA complex synthesised using the protocol of Isobe⁴⁶ was investigated as a zinc(II) source (entry 6) but no yield

improvement was obtained from the use of this less THF-soluble complex.

It is known that the (*N,N*-diethylcarbamoyloxy) group ranks more highly than the methoxymethyl (MOM) group in the DoM hierarchy;^{47,48} DMPU (12% v/v) was added to mimic the ability of the carbamate moiety of **3b** to de-aggregate and increase the reactivity of the metal amide base (entry 7).^{49–51} The presence of the co-solvent resulted in full conversion of **3a**, a higher isolated yield and a reduced reaction time. A range of co-solvent concentrations (12–65% v/v) were screened; however, it was observed that DMPU concentrations above 12% v/v yielded similar conversions and isolated yields. This much improved procedure was adopted as the standard protocol for generating styrenes from acetal **3a**.



The effect of the co-solvent appears to be on the dehydrofluorination/metallation. Given that DMPU is unnecessary for good conversion of **3b** to **9b**, the carbamate was ideal to probe this effect. Generation of vinylzinc **9b** in the presence of 12% v/v (or higher proportion of) DMPU resulted in 100% conversion and subsequent Negishi coupling with **11k** afforded styrene **12bk** in 33% isolated yield. The same procedure without the co-solvent resulted in a similar 36% isolated yield, establishing that DMPU does not have any effect on the efficiency of the coupling step. We were also able to shorten the reaction time for the coupling step from 16 to 0.5 h without any reduction in yield; in some cases, the shorter time was advantageous (*vide infra*). During the course of this investigation, we were pleased to find that the reactions could be carried out smoothly using commercial LDA as a solution in THF/heptane/ethylbenzene, further simplifying our protocol.



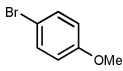
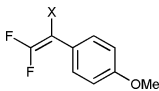
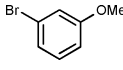
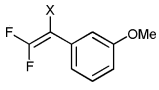

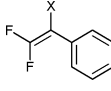
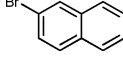
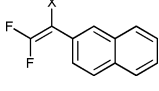

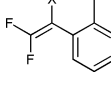
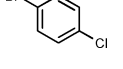
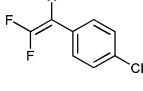
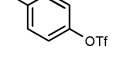
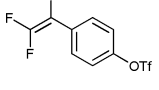
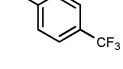
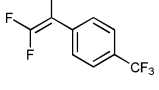
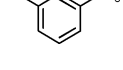
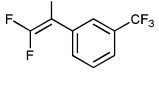
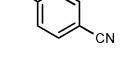
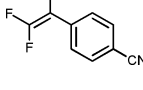
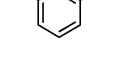
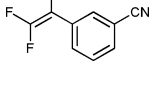
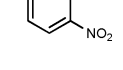
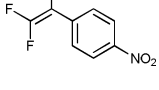
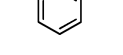
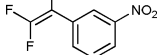
Scheme 3

Table 1 Optimising the reaction conditions for dehydrofluorination/metallation and coupling of **3a**

Entry	LDA (eq.)	Zn salt (eq.)	Time at		Conversion ^a (%)	Yield ^b (%)
			0 °C (h)	15–18 °C (h)		
1	2.0	1.0	1	1	27	—
2	2.5	1.1	1	2.5	65	—
3	2.5	1.1	1	4	67	—
4	3.0	1.1	1	4	93	34
5	2.5	1.1	0	4	88	—
6	2.5	1.1 ^c	1	3	81	47
7 ^d	2.5	1.1	1	1	95	60

^a Measured by integration of the ¹⁹F NMR spectrum. ^b Isolated yield of **12aa** after chromatography. ^c ZnCl₂·TMEDA complex was used. ^d The solvent was 12% v/v DMPU/THF.

Table 2 Scope and limitations of the Negishi coupling protocol

Halide		Precursor	Method ^d	Product (overall yield)	
11a		3a 3b	a b		12aa , X = OMEM (60%); 12ba , X = ODEC (65%).
11b		3a 3b	a b		12ab , X = OMEM (73%); 12bb , X = ODEC (63%).
11c		3a 3b	a b		12ac , X = OMEM (53%); 12bc , X = ODEC (65%).
11d		3a 3b	a b		12ad , X = OMEM (48%); 12bd , X = ODEC (57%).
11e		3a 3b	a b		12ae , X = OMEM (40%); 12be , X = ODEC (0%).
11f		3a 3b	a b		12af , X = OMEM (54%); 12bf , X = ODEC (51%).
11g		3a 3b	a ^a b ^a		12ag , ^b X = OMEM (25%); 12bg , ^b X = ODEC (60%).
11h		3a 3b	a b		12ah , ^b X = OMEM (41%); 12bh , ^b X = ODEC (53%).
11j		3a 3b	a ^a b		12aj , X = OMEM (20%); 12bj , X = ODEC (37%).
11k		3a 3b	a ^a b		12ak , X = OMEM (25%); 12bk , X = ODEC (36%).
11l		3a 3b	a ^a b		12al , ^b X = OMEM (33%); 12bl , ^b X = ODEC (29%).
11m		3a 3b	a b ^c		12am , ^b X = OMEM (41%); 12bm , ^b X = ODEC (42%).
11n		3a 3b	a ^a b		12an , ^b X = OMEM (31%); 12bn , X = ODEC (18%).

^a Coupling reaction time 0.5 h. ^b Commercial LDA was used. ^c Coupling reaction time 0.25 h. ^d Method a: i) from **3a**, LDA (2.5 eq.), ZnCl₂ (1.1 eq.), 12% v/v DMPU/THF, 0 °C (1 h) then 15 °C (1 h), then ii) aryl halide, Pd(PPh₃)₄, 65 °C, 16 h. Method b: i) from **3b**, LDA (2.5 eq.), ZnCl₂ (1.1 eq.), THF, 0 °C (1 h) then 15 °C (1 h), then ii) aryl halide, Pd(PPh₃)₄, 65 °C, 16 h.

Table 3 Coupling method comparison for selected substrates

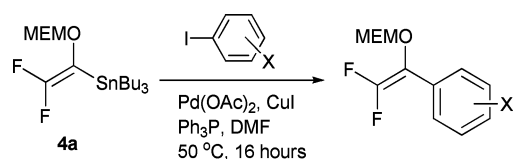
Product	Coupling method (% isolated overall yield from 3a)		
	Negishi ^a	Suzuki ^b	Stille ^c
12aa	4-OMe 60	50	50
12ab	3-OMe 73	55	(-) ^c
12ae	2-Me 40	48	(-) ^c
12ag	4-OTf 25	36 ^d	67
12ah	4-CF ₃ 41	53	(-) ^c
12ak	4-CN 25	(-) ^c	46
12am	4-NO ₂ 41	(-) ^c	61
12an	3-NO ₂ 31	0	(-) ^c

^a This study. ^b Ref. 36 ^c Not done. ^d Ligand-free procedure (see text).

Scope and limitations

With high conversion conditions in hand for both **3a** and **3b**, the scope of the Negishi coupling could be explored with a palette of aryl bromides and iodides **11a–11n**. Table 2 summarises the results. These reactions were usually carried out by preparing a batch of the organozinc reagent and transferring the appropriate quantity by syringe to reaction tubes. Organozinc reagents are sometimes avoided because of their sensitivity to moisture and are usually formed *in situ* for immediate consumption; however, Leitner and co-workers discovered that a solution of 2-pyridylzinc bromide could be stored for more than 12 months at room temperature without any significant decomposition.⁵² A solution of reagent **9b** was stored in the refrigerator for 7 days prior to Negishi coupling with **16a** using the standard conditions. A 65% yield of styrene **12ba** was obtained from a coupling carried out at the end of that period, revealing that **9b** is relatively stable in solution, and certainly amenable to batch preparation.

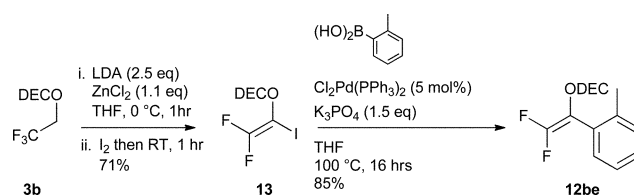
Pleasingly, the total yield of coupling product from **3a** is competitive with that from the Suzuki–Miyaura protocol (which required a low temperature step) described by Katz and co-workers. Table 3 highlights some interesting comparisons between the two methods with benchmark Stille couplings from **4a**; these were carried out according to Scheme 4. The Suzuki yields in Table 3 were taken from the paper of Katz *et al.*, with the exception of **12ag**. For this substrate, we adapted the published procedure by running the coupling reaction with a Pd(dba)₂ (5 mol%) catalyst (instead of the published PdCl₂) in *n*-propanol containing triethylamine, and without the expensive bulky monophosphine ligand RuPhos. This allowed us to generate **12ag** in 36% overall yield from **3a** (the addition of RuPhos did not increase the yield).



Scheme 4

Our Negishi method is at least competitive with the Suzuki–Miyaura protocol and has the great advantage of requiring no cooling beyond ice bath temperature; this has strategic implications for the scalability of our methodology. It is interesting that the nitro-congener **12an** could not be synthesised by Suzuki coupling of trifluoroborate **8**, whereas our Negishi protocol

delivers **12an** in 31% yield. In general, π -electron rich and neutral aryl halides couple with both **9a** and **9b** in moderate to good yields. The most successful coupling partners were 3-(methoxy)- and 4-(methoxy)bromobenzene. The potential for scale up was demonstrated with 4-chloro species **11f**; only a slightly lower yield of **12bf** (38%) was obtained when the coupling reaction was scaled to 10 mmol. Suzuki–Miyaura coupling of aryl chlorides can now be effected in the presence of bulky phosphine ligands,⁵³ so these intermediates may be a potential entry point to the difluoromethylketone libraries. Only one result suggested a clear difference between **9a** and **9b** as coupling partners. Product **12ae** was generated in 40% yield from 2-bromotoluene; however, attempts to couple carbamate **9b** with **11e** were unsuccessful. Interchanging the transmetallating and oxidative addition species^{54–56} by using a Suzuki coupling reaction between iodide **13** and (*o*-tolyl)boronic acid afforded styrene **12be** in 60% overall yield from **3b**, suggesting that transmetallation from **9b** to an (*o*-tolyl)palladium phosphine complex may be slow (Scheme 5). We were able to improve upon the previous⁴³ low temperature generation of **13** by quenching **9b** (generated close to ambient temperature) with a solution of iodine in THF. Aryl halides containing electron withdrawing groups generally coupled less efficiently, though there were some notable exceptions. Our initial investigations used 1-iodo-4-nitrobenzene⁵⁷ in the standard procedure; after stirring for 16 h at 65 °C, the ¹⁹F NMR spectrum of the crude reaction mixture revealed only traces of desired styrene **12bm**. Previous evidence that the Negishi coupling to generate methoxystyrene **12ba** was complete after 30 min prompted a short GC-MS study to derive a crude profile of the coupling of **11m** and **9b**. The reaction was undertaken as normal and an aliquot was removed every 15 min for 1 h. These aliquots were exposed to a crude work-up, then GC-MS analysis was performed, revealing a complex mixture. This is in contrast to the clean spectra obtained for the generation of methoxystyrene **12ba**. Even after 16 h no degradation products developed, indicating that **12ba** is much more robust than **12bm**. Not all of the species could be identified, but styrene **12bm** was present, with HF adduct **14**,⁵⁸ protonated species **15** and unreacted **11m**. After 15 min a significant quantity of styrene **12bm** was produced, but the quantity seemed to remain constant for the monitoring period of 60 min. After stirring for 16 h at 65 °C, a significant reduction in the concentration of **12bm** was observed by GC-MS. A considerably improved isolated yield of 42% was achieved when the reaction was quenched after just 15 min. Although significant quantities of the coupled products can be obtained from **11m** and **11n**, purification is difficult and contamination with some unidentifiable material is apparent (~95% purity by NMR), representing a limit to the current Negishi methodology. The improvement in yield brought about by shortening the reaction time was not general for all π -electron deficient aryl halides. Only a few returned better yields



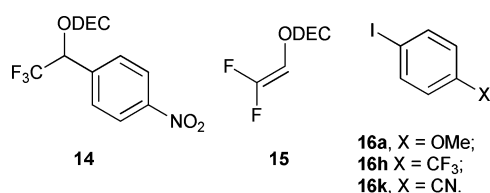
Scheme 5

Table 4 Comparison of coupling efficiencies of aryl iodides and bromides

Aryl halide	Coupling partner (Yield%)	
	9a ^a	9b ^b
11a	60	65
16a	58	65
11h	41	53
16h	29	53
11k	22	36
16k	22	32

^a i) from **3a**, LDA (2.5 eq.), ZnCl₂ (1.1 eq.), 12% v/v DMPU/THF, 0 °C (1 h) then 15 °C (1 h), then ii) aryl halide, Pd(PPh₃)₄, 65 °C, 16 h. ^b i) from **3b**, LDA (2.5 eq.), ZnCl₂ (1.1 eq.), THF, 0 °C (1 h) then 15 °C (1 h), then ii) aryl halide, Pd(PPh₃)₄, 65 °C, 16 h.

after quenching the reaction at 30 min. *para*-Trifluoromethyl styrenes **12ah** and **12bh** were generated in moderate yield, as were the cyano derivatives **12ak**, **12bk**, **12al** and **12bl**. Yields of triflates **12ag** and **12bg** were also improved when the reaction time was reduced to 30 min. While all three methods are competitive for the formation of **12aa**, the Stille coupling with π -electron deficient aryl iodides delivers the best yields. The general trends observed in the Negishi results are similar to those obtained by Burton and co-workers³⁸ for trifluorostyrene synthesis from HFC-134a and aryl iodides, with the highest yields obtained using π -electron rich aryl iodides, and lower yields obtained when the arene was π -electron deficient. We also compared aryl bromide and iodide coupling partners in selected cases (Table 4), finding no advantage in the use of the more reactive iodides; the isolated purified yields are comparable or better with the bromides. As aryl iodides would be expected to undergo oxidative addition significantly faster than the analogous bromides, it would appear that oxidative addition is not the rate-determining step in the catalytic cycle. This is an observation that will be investigated further within our laboratory, but lies beyond the scope of this manuscript; however, it is clear that no advantage accrues from the use of the iodides. Coupling a range of aryl chlorides was not attempted as 4-(methoxy)chlorobenzene did not couple with **9a** under our standard Negishi conditions. Finally, we carried out a limited number of experiments generating **9a** in the presence of magnesium chloride and then coupling, but we saw no significant and consistent increase in reaction yield over the zinc-only protocol (see the Supplementary Information† for more details).^{39,40} The continuing value of the Stille coupling is shown in Table 3; the Stille coupling reaction may still be the most effective protocol when the aryl component is more costly than the stannane, but the yield advantage must be weighed against the toxicity of the organotin reagent and waste. The Negishi method is competitive because it avoids toxic reagents, is direct and can be implemented close to ambient temperature.

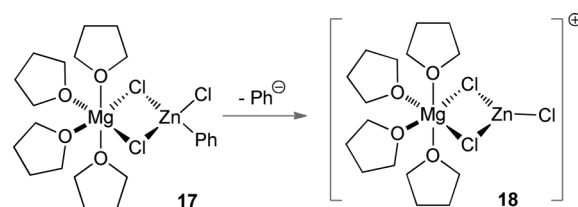


This Negishi protocol clearly offers some distinct advantages over the related Suzuki–Miyaura and Stille coupling methods. Access to the alkenylzinc coupling partner is achieved *in situ*

at 0 °C, eliminating the cost of low temperature chemistry and removing an isolation step. These are obvious advantages if scale-up is anticipated. As with the Suzuki–Miyaura method, however, overall yields of π -electron deficient styrenes were moderate to poor. Use of stannane **4a** improved these overall yields and demonstrated that Stille coupling is a robust and viable option when other approaches are less available. Though stannane synthesis currently requires low temperature conditions, the Stille coupling of **4a** is so reliable that it may be the preferred protocol for coupling partners of value.

On the relationship between structure and reactivity in the organozinc reagents

While our understanding of the relationship between organozinc constitution and structure, and reactivity in coupling reactions is still in its infancy, the recent work of Lei and co-workers,³⁹ Hevia⁴⁰ and Organ⁴¹ has begun to reveal the complexity inherent in Negishi coupling chemistry. The importance of organozincate species is becoming established and the nature of the nucleophilic reagent (organozinc or organozincate) appears to control which step determines the rate. Lei and co-workers recorded reaction kinetics (followed by IR spectroscopy), and interpreted the results with a set of simple DFT calculations to attempt to identify the organozinc species from which the organic ligand would transfer most rapidly. The calculations involved separating the Zn–C bond to produce an ion pair; geometries were optimised (B3LYP/6-31G*, gas phase), and electronic energies were also calculated as single points using a simple model for THF solvation. Scheme 6 shows the reaction considered; mixed metal complex **17** (generated from Grignard reagent) has a much lower (electronic) energy of ion pair separation to **18** (and phenyl anion) than any of the other species considered (gas phase or THF).

**Scheme 6**

Complex **17** was also characterised by X-ray structure elucidation from single crystals. We have invoked the coordinating abilities of MEM and carbamoyl groups to explain the ease with which **9a** and **9b** (and their organolithium precursors) form and we were interested in anticipating the effects of these groups upon the ease of alkenyl ligand transfer from zinc. We therefore carried out some modelling for **17**, **18** and **19–22** using Spartan'08⁵⁹ (B3LYP/LACP*(6-31G*)) to produce preliminary structures, and Gaussian'09⁶⁰ [(B3LYP/SDD(6-31G*))] for reoptimisation and frequency calculations in the gas phase.⁶¹ The geometry of the [(THF)₄MgZnCl₃] cation **18** was found by ablating the phenyl group and minimising the structure. Lei calculated a value of 155 kcal mol⁻¹ for E_{transfer} from **17**; we obtained the very similar value of 151.5 kcal mol⁻¹. The difference is due to a lower energy being obtained for the phenyl anion. Given the failure of any advantage to accrue from the presence of magnesium(II) chloride

in our couplings, we will consider only the monomeric and dimeric zinc complexes, rather than complexes analogous to **17**.

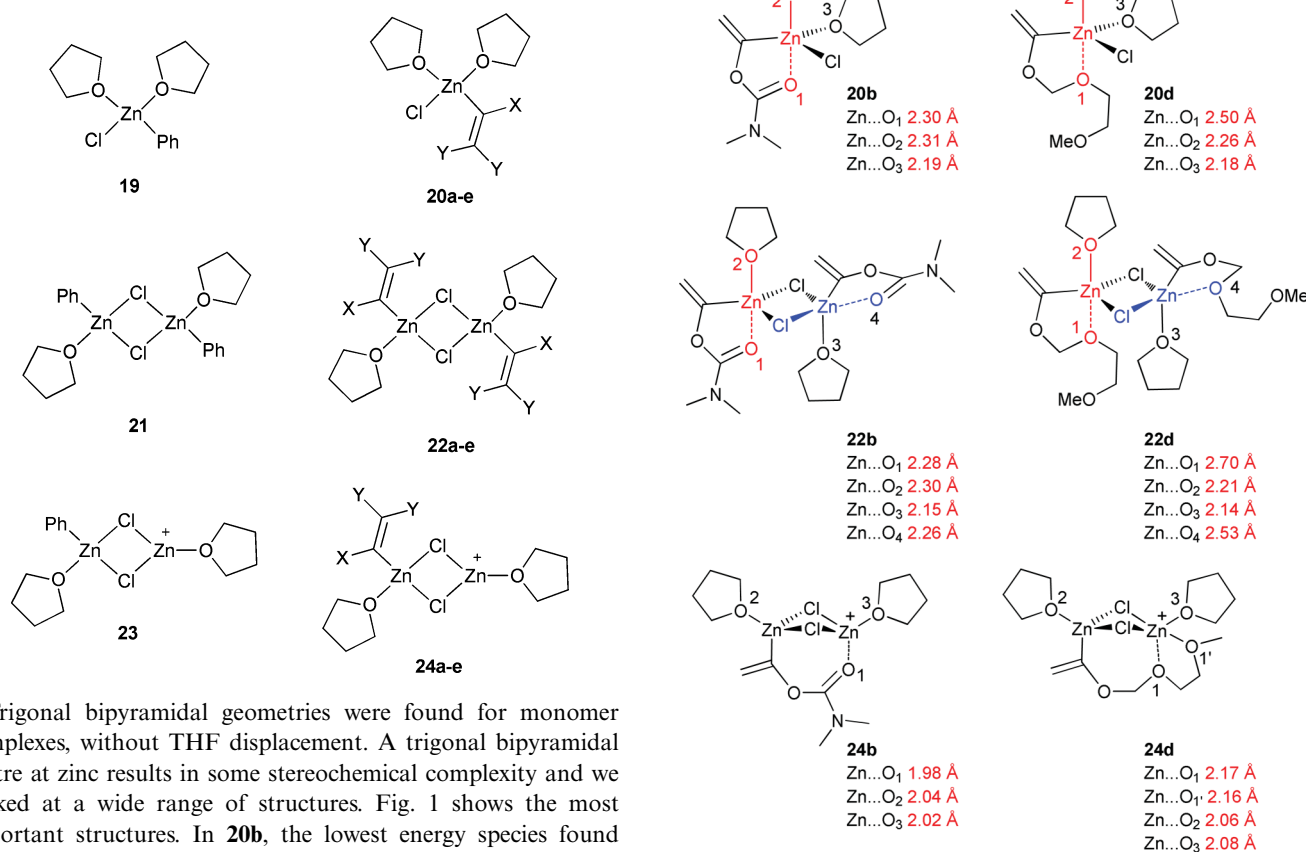


Fig. 1 Complex geometries used for the electronic structure calculations. Red/blue atom labelling is used to identify the apical ligands at each zinc centre. Distances were measured from the B3LYP/LACVP*(6-31G*) structures.

Trigonal bipyramidal geometries were found for monomer complexes, without THF displacement. A trigonal bipyramidal centre at zinc results in some stereochemical complexity and we looked at a wide range of structures. Fig. 1 shows the most important structures. In **20b**, the lowest energy species found for this complex (and one to which a number of quite different stereoisomers optimised), the Zn...O=C(carbamate) distance is 2.38 Å, the same as the apical (THF)O...Zn distance and only 0.2 Å longer than the equatorial (THF)O...Zn distance. The bite angle (C–Zn...O) of the ligand is 76° so the occupancy of one apical and one equatorial site represents the ideal disposition. The trigonal bipyramidal geometry in **20b** is slightly distorted; the (THF)O–Zn...O=C(carbamate) angle (the oxygens are apical) is 167°, and the angles between the equatorial bonds are not equal. In **20d**, the Zn...OCH₂O distance is longer at 2.74 Å and the angle made between the apical oxygen atoms at zinc is slightly wider at 172° in consequence.⁶⁷ Structures in which the potential coordinating group was placed as far as possible from the metal centre always brought the group into coordination during the optimisation. These are gas phase calculations, so they do not anticipate the presence of bulk coordinating solvent and it may be that THF molecules replace our coordinating groups in solution. However, chelate formation is highly entropically favourable because a solvent molecule is released and given that the concentration of pure THF is only 12 M at 20 °C, it may be these species are chelated even in THF solution.

Alkenyl transfer then affords the cationic [(THF)₂ZnCl]⁺ species as in the reaction considered by Marder. Alkenyl transfer is less favourable than phenyl transfer by *ca.* 14 kcal mol⁻¹ from monomer or dimer. In the monomers, the introduction of a carbamoyloxy group (ODMC) or a OMEM group lowers the values of E_{transfer} by 18.6 (from **20b**) and 16.9 kcal mol⁻¹ (from **20d**), respectively. In each case difluorination brings about a further lowering in energy (a further 9.5 kcal mol⁻¹ from **20b** to **20c**, and 10.7 kcal mol⁻¹

from **20d** to **20e**) so the effect of the fluorine atoms is only slightly smaller than those of the chelating groups. These lower values of E_{transfer} must arise from destabilisation of the neutral complexes, or inductive stabilisation of the anionic fragment in the ion pair, or both. The dimeric species presented considerable stereochemical complexity, though a key observation allowed us to simplify the range of structures which required examination. We found that the coordinating groups tended to bridge across to the cationic zinc during optimisation of cations **24**, illustrated by **24b** and **24d** in Fig. 1. For this reason, we used the lowest energy dimer complexes which present the coordinating group in an orientation from which it can reach across to the cationic zinc centre.

The coordinated oxygen is apical in these complexes with an equatorial C–Zn bond and μ -bridging *via* equatorial chlorine atoms. The lowest energy dimer complexes were unsymmetrical around the Zn₂Cl₂ core, locating the chelating groups in distinct environments; carbamate and MEM O...Zn distances were similar to those in the monomers.

In the bridged cations, the O...Zn distances shorten (consistent with the cationic nature of the zinc centre) at 1.98 Å for the μ -bridging carbamoyloxy group (Zn...O₁ in **24b**), and 2.17 and 2.16 Å for the two MEM oxygens (Zn...O₁ and Zn...O₁' respectively in **24d**) (both Fig. 1). The effect of fluorination on

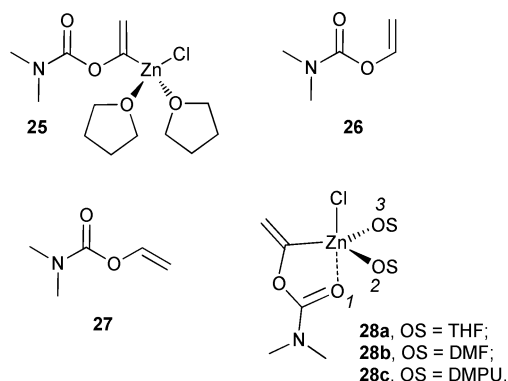
Table 5 Ligand transfer energies (E_{transfer}) calculated for monomeric and dimeric alkenylzinc chlorides

Transferring ligand	X	Y	E_{transfer} (Kcal mol ⁻¹) ^a			
			Monomer		Dimer	
Phenyl ³⁰	—	—	19	182.2	21	183.6
Phenyl ^a	—	—	19	179.5	21	181.2
Alkenyl	H	H	20a	193.3	22a	193.9
	ODMC	H	20b	174.7	22b	156.7
	ODMC	F	20c	165.2	22c	147.1
	OMEM	H	20d	176.4	22d	155.0
	OMEM	F	20e	165.7	22e	144.5

^a B3LYP/SDD(6-31G*), gas phase (Gaussian'09); DMC = CONMe₂.

E_{transfer} is still around 10 kcal mol⁻¹, and while there is a clear difference between the carbamate and acetal series in terms of geometry, with both oxygens in the methoxyethoxy chain recruited (**24d** and **24e**), the net effects of the OMEM and ODMC groups on E_{transfer} are very similar at 49 and 47 kcal mol⁻¹ respectively. Both the carbamate and MEM dimer complexes have E_{transfer} values comparable to the value calculated for phenyl complex **17**.

The formation of pentacoordinate species requires some comment because tetrahedral coordination is well established for zinc(II).⁶² Jackson and co-workers have used a higher level of theory [B3LYP/SDD(6-311G**)] to distinguish between pentacoordinate and tetra-coordinate geometries for alkylzinc iodides in DMF.⁶³ Monomer complex **20b** was therefore examined at this level of theory and the integrity of the pentacoordinate geometry was maintained. Non-coordinated tetrahedral geometry **25** (Fig. 2) was also optimised using Jackson's method [B3LYP/SDD(6-311G**)]. The pentacoordinate species is 6.6 kcal mol⁻¹ more stable than **27** at this level of theory.⁶⁴ Part of this energy difference is steric in origin and can be revealed by considering the enol carbamate alone; conformer **26** is 3.7 kcal mol⁻¹ less stable than **27** (B3LYP/6-311G**). The remainder of the energy difference (3 kcal mol⁻¹) represents the favourable (presumably electrostatic) interaction between carbamate oxygen and zinc. This is a very modest energy difference and it indicates that the conclusions drawn from Table 5 will be affected minimally whether the organozinc species are tetra- or pentacoordinate.

**Fig. 2** Complexes used to probe the effect of chelation and pentacoordination at zinc.

To explore the effect of solvent donor ability on the integrity of the pentacoordinate geometry, we examined slightly less stable

Table 6 Selected interatomic distances for complexes **28a–28c**

Structure	Interatomic distances (Å)		
	Zn...O ₁	Zn...O ₂	Zn...O ₃
28a	2.77	2.14	2.19
28b	2.49	2.13	2.13
28c	2.86	2.08	2.14

symmetrical trigonal bipyramidal complexes **28a–28c** (**20b** is 3.6 kcal mol⁻¹ more stable than **28a** [B3LYP/SDD(6-311G**)]); starting from a less stable geometry might predispose the trigonal bipyramid to collapse to a tetrahedral structure. Replacing the two THF molecules with DMF or DMPU failed to labilise the pentacoordinate structure, though there are changes in interatomic distances (Table 6). Interestingly, the distance between the carbamate oxygen and the zinc centre is shortest when DMF ligates the metal, though the DMF oxygens are neither closer nor more distant from the zinc than those of the other solvents.

The status of the cation-stabilising interactions cannot be evaluated without a more rigorous treatment of solvation, but it seems that the coordinating groups may have a significant role to play in the organozinc chemistry. These are interesting predictions which cannot be evaluated using reaction yields, and more detailed calculations and kinetic investigations lie outwith the scope of this manuscript.⁶⁵ It is certain that more useful insights will only evolve once the entire pathway *via* transmetallation and reductive elimination can be modelled,⁶⁶ and of course, strongly coordinating groups and solvents may influence those steps. We propose to investigate these aspects of the reaction pathway and will report our findings elsewhere.

Conclusions

We have developed a dehydrofluorination/metallation and Negishi coupling procedure that brings useful C–C bond forming chemistry from trifluoroethanol derivatives away from the low temperature regimes (–78 °C or below) required previously and up to near ambient temperature. This is a major strategic advance in the synthesis of selectively fluorinated molecules, enabled by the seminal contribution of Burton. Our method delivers yields of coupling products competitive with those reported by Katz and co-workers, while using fewer preparative steps and avoiding low temperature conditions entirely. Batches of the key organozinc reagents were successfully prepared and stored, highlighting the chemistry's utility for parallel synthetic applications. The use of commercial LDA solution is an additional attractive feature. The presence of the coordinating groups in these complexes may have interesting consequences for the structure and reactivity of the organozinc species; using an accepted method of theory with a large basis set, we have found favourable pentacoordinate structures, where only tetrahedral structures were anticipated. Preliminary electronic structure calculations predict that transmetallation from zinc to palladium may be assisted by the –OMEM and –ODEC groups at the α-position; the presence of two fluorine atoms appears to result in a similar effect. The electrophilicity of the coupling products and the vulnerability of certain types of products towards HF addition may ultimately impose limitations upon the type of coupling reactions that can

be executed; nevertheless, a range of valuable new chemistries accessible close to ambient temperature may be made available by these discoveries with profound strategic consequences for the synthesis of selectively difluorinated molecules at scale.

Experimental

Batch generation of alkenylzinc reagents

2,2-Difluoro-1-(*N,N*-diethylcarbamoyloxy)ethenylzinc chloride 9b. Lithium diisopropylamide (17.9 cm³ of a 1.4 M solution in THF) was added dropwise to a solution of 2,2,2-trifluoroethyl carbamate **3b** (1.99 g, 10 mmol, 1.63 cm³), freshly fused zinc chloride (1.5 g, 11 mmol) in dry THF (20 cm³) at 0 °C over a period of 10 min. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature, to afford **9b** (assumed to be a 0.25 M solution in THF). The appropriate volume was then used for each Negishi coupling reaction.

2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)ethenylzinc chloride 9a. Lithium diisopropylamide (17.9 cm³ of a 1.4 M solution in THF) was added dropwise to a solution of 2,2,2-trifluoroethyl acetal **3a** (1.88 g, 10 mmol, 1.55 cm³), freshly fused zinc chloride (1.5 g, 11 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (5 cm³) in dry THF (20 cm³) at 0 °C over a period of 10 min. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature, to afford **4a** (assumed to be a 0.22 M solution in DMPU/THF). The appropriate volume was then used for each Negishi coupling reaction.

Typical coupling procedure with alkenylzinc reagents 9a and 9b

2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-methoxyphenyl) ethene 12aa. Alkenylzinc reagent **9a** (4.45 cm³ of a 0.22 M solution in THF/DMPU) was added in one portion to a flask containing 4-bromoanisole **11a** (206 mg, 1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and the mixture was heated at 65 °C overnight. The black mixture was cooled to room temperature, diluted with DCM (30 cm³) and water (40 cm³) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (30% diethyl ether in light petroleum ether) to afford styrene **12aa** (170 mg, 60%) as a yellow oil; *R*_f (40% diethyl ether in light petroleum ether) 0.30; ν_{\max} (film)/cm⁻¹ 2936, 1737, 1611, 1515, 1465, 1257, 1179, 1151, 1035, 979, 950, 836; δ_{H} (400 MHz, CDCl₃) 3.40 (3 H, s, CH₂OCH₃), 3.56–3.60 (2 H, m, OCH₂CH₂O), 3.84 (3 H, s, ArOCH₃), 3.85–3.90 (2 H, m, OCH₂CH₂O), 4.87 (2 H, s, OCH₂O), 6.90–6.96 (2 H, m, Ar*H*), 7.38–7.43 (2 H, m, Ar*H*); δ_{C} (100 MHz, CDCl₃) 54.8, 58.5, 67.9, 71.1, 94.6 (t, ⁴*J*_{C-F} 2.8), 113.5, 114.8 (dd, ²*J*_{C-F} 36.1, 18.7), 121.5 (br. d, ³*J*_{C-F} 5.8), 127.9 (dd, ⁴*J*_{C-F} 5.3, 3.8), 154.6 (app. t, ¹*J*_{C-F} 287.4), 159.1; δ_{F} (376 MHz, CDCl₃) –99.9 (1 F, d, ²*J*_{F-F} 61.5), –108.5 (1 F, d, ²*J*_{F-F} 61.5); [HRMS (ES-TOF, [M + Na]⁺) Found: 297.0901; Calc. for C₁₃H₁₆O₄F₂Na: 297.0914; *m/z* (CI) 292 (100%, [M + NH₄]⁺), 199 (5), 169 (40); GC (98%) *t*_R 13.81 min (60–300 °C, 10 °C min⁻¹).

1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-methoxyphenyl) ethene 12ba. Styrene **12ba** was prepared from **9b** (3.95 cm³ of a 0.25 M solution in THF), 4-bromoanisole **11a** (206 mg,

1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) at 65 °C overnight. The previous work-up, isolation and purification afforded styrene **12ba** (185 mg, 65%) as a pale yellow oil; *R*_f (40% diethyl ether in light petroleum ether) 0.35; λ_{\max} (MeOH)/nm 250 (ϵ /dm³ mol⁻¹ cm⁻¹ 17 400); ν_{\max} (film)/cm⁻¹ 1729, 1611, 1515, 1425, 1269, 1147, 1035, 983, 838, 824, 786, 756; δ_{H} (400 MHz, CDCl₃) 1.20 (3 H, t, *J* 7.1, NCH₂CH₃), 1.27 (3 H, t, *J* 7.1, NCH₂CH₃), 3.38 (2 H, q, *J* 7.1, NCH₂CH₃), 3.46 (2 H, q, *J* 7.1, NCH₂CH₃), 3.83 (3 H, s, OCH₃), 6.91–6.95 (2 H, m, Ar*H*), 7.35–7.39 (2 H, m, Ar*H*); δ_{C} (100 MHz, CDCl₃) 12.7, 13.7, 41.4, 42.0, 54.8, 111.7 (dd, ²*J*_{C-F} 38.9, 19.5), 113.6, 122.1 (br. d, ³*J*_{C-F} 6.3), 126.6 (dd, ⁴*J*_{C-F} 6.0, 3.3), 152.5, 154.1 (app. t, ¹*J*_{C-F} 288.1), 158.9; δ_{F} (376 MHz, CDCl₃) –95.9 (1 F, d, ²*J*_{F-F} 54.4), –106.0 (1 F, d, ²*J*_{F-F} 54.4); [HRMS (EI, M⁺) Found: 285.118829; Calc. for C₁₄H₁₇F₂NO₃: 285.117650]; *m/z* (CI) 286 (40%, [M + H]⁺), 169 (90), 100 (100); GC (98%) *t*_R 12.50 min (70–250 °C, 20 °C min⁻¹).

Effect of order of addition on the preparation of 1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(4'-methoxyphenyl) ethene 12ba

Procedure 1: Addition of LDA/Zn(II) chloride mixture to 3b. LDA (3.9 cm³ of a 0.64 M solution) was added dropwise to a solution of freshly fused zinc(II) chloride (150 mg, 1.1 mmol) in THF (2 cm³) at 0 °C over a period of 5 min and the mixture was left to stir for 1 h. This solution was then cannulated into a solution of **3b** (199 mg, 1.0 mmol) in THF (1 cm³) and stirred for 1 h at 0 °C, then for 1 h at room temperature (15–18 °C). The solution turned orange and was cannulated onto a mixture of 4-iodoanisole (257 mg, 1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and stirred at 65 °C overnight. The black mixture was cooled to room temperature and diluted with DCM (30 cm³) and water (40 cm³) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and purified by flash column chromatography on silica (30% diethyl ether in light petroleum ether) to afford styrene **12ba** (145 mg, 51%) as a pale yellow oil; the data were in agreement with those reported earlier.

Procedure 2: Addition of 3b to LDA/zinc(II) chloride mixture

A solution of **3b** (199 mg, 1.0 mmol) in THF (1 cm³) was added dropwise to a mixture of freshly fused zinc(II) chloride (150 mg, 1.1 mmol) and LDA (3.9 cm³ of a 0.64 M solution) in THF (2 cm³) at 0 °C over a period of 5 min. The mixture was stirred for 1 h at 0 °C, then for 1 h at room temperature (15–18 °C). The brown solution was then cannulated onto a mixture of 4-iodoanisole **16a** (257 mg, 1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and stirred at 65 °C overnight. The usual work-up and purification afforded styrene **12ba** (74 mg, 26%) as a pale yellow oil; the data were in agreement with those reported earlier.

1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-methoxyphenyl) ethene 12ba; preparation using *tert*-butyllithium. *tert*-Butyllithium (1.18 cm³ of a 1.7 M solution) was added dropwise to a solution of carbamate **3a** (200 mg, 1 mmol) in THF (5 cm³) over a period of 5 min at –78 °C. The colourless solution was stirred for 30 min, turning from colourless to orange to deep blue. A solution of freshly fused zinc(II) chloride (150 mg, 1.0 mmol) in THF (2 cm³) was added in one portion at –78 °C and the blue

solution was allowed to warm to room temperature over a period of 1.5 h, turning yellow during this time. The yellow solution was cannulated onto a mixture of *tetrakis*(triphenylphosphino)palladium(0) (58 mg, 0.05 mmol) and 4-iodoanisole (257 mg, 1.1 mmol) and the solution was stirred at 65 °C overnight. The reaction mixture was diluted with diethyl ether (40 cm³) and water (40 cm³) and filtered through a short pad of Celite. The organic phase was separated, dried (MgSO₄) and concentrated under reduced pressure to a dark brown oil. Purification by flash column chromatography on silica (30% diethyl ether in light petroleum ether) afforded styrene **12ba** as a pale yellow oil (*ca.* 70%, the isolated compound being contaminated with some hydrocarbon from the eluent). The data were in agreement with those reported earlier.

1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-cyanophenyl)ethene 12bk using DMPU co-solvent. Lithium diisopropylamide (1.47 cm³ of a 1.7 M solution in THF) was added dropwise to a solution of 2,2,2-trifluoroethyl carbamate **3b** (0.199 g, 1 mmol), freshly fused zinc chloride (0.150 g, 1.1 mmol) in dry THF (2 cm³) and freshly distilled DMPU (0.5 cm³) at 0 °C over a period of 10 min. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature, to afford **9b** (assumed to be a 0.25 M solution in THF). The solution of **9b** was then added in one portion to a flask containing 4-bromobenzonitrile **11a** (200 mg, 1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and the mixture was heated at 65 °C for 1 h. The black mixture was cooled to room temperature, diluted with DCM (15 cm³) and water (15 cm³) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was passed through a short pad of silica with hexane (100 cm³). The solvent was removed under reduced pressure and crystallisation was encouraged by addition of hexane. The pale yellow solid was washed with hexane to reveal styrene **12aa** (93 mg, 33%); *R*_f (40% diethyl ether in light petroleum ether) 0.23; mp 80–82 °C; (Found: C, 60.55; H, 4.99; N, 9.57; C₁₄H₁₄F₂N₂O₂ requires C, 60.00; H, 5.03; N, 9.57%); *v*_{max}(film)/cm⁻¹ 2967, 2932, 2229, 1720, 1415, 1269, 1146, 982, 846, 822; δ_{H} (400 MHz, CDCl₃) 1.20 (3 H, t, *J* 7.2, NCH₂CH₃), 1.29 (3 H, t, *J* 7.2, NCH₂CH₃), 3.38 (2 H, q, *J* 7.2, NCH₂CH₃), 3.48 (2 H, q, *J* 7.2, NCH₂CH₃), 7.53 (2 H, br. d, *J* 8.3 Ar*H*), 7.69 (2 H, br. d, *J* 8.3 Ar*H*); δ_{C} (100 MHz, CDCl₃) 12.7, 13.7, 41.6, 42.3, 111.1, 111.2 (dd, ²*J*_{C-F} 37.4, 20.3), 117.9, 125.2 (dd, ⁴*J*_{C-F} 7.4, 3.7), 131.8, 134.5 (br. d, ³*J*_{C-F} 7.4), 152.0, 154.9 (app. t, ¹*J*_{C-F} 294.0); δ_{F} (376 MHz, CDCl₃) -89.3 (1 F, d, ²*J*_{F-F} 39.1), -99.3 (1 F, d, ²*J*_{F-F} 39.1); [HRMS (APCI, [M + H]⁺) Found: 281.1089; Calc. for C₁₄H₁₅N₂O₂F₂: 281.1102]; *m/z* (CI) 321 (8), 309 (20%, [M + C₂H₅]⁺), 281 (100%, [M + H]⁺), 100 (20); GC (98%) *t*_R 12.62 min (70–320 °C, 20 °C min⁻¹).

Typical Stille coupling procedure for styrene synthesis

2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-[4'-(trifluoromethanesulfonyloxy) phenyl] ethene 12ag. A mixture of copper(I) iodide (0.170 g, 0.89 mmol), triphenylphosphine (0.105 g, 0.40 mmol) and palladium(II) acetate (24 mg, 0.11 mmol) was pump-purged twice with argon, then dry, degassed DMF (45 cm³) was added. A solution of iodotriflate **11g** (0.936 g, 4.0 mmol) in DMF (2 cm³) was added and the mixture was heated to 50 °C.

Stannane **4a** (1.83 g, 4.0 mmol) was then added and the mixture was stirred for 16 h at this temperature. The mixture was allowed to cool to ambient temperature and diluted with diethyl ether (20 cm³) and water (100 cm³). KF was added (6 cm³ of a 0.91 M aqueous solution) and the mixture was stirred rapidly for 30 min, then filtered under suction to remove the grey precipitate. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 25 cm³). The original organic layer and the extracts were combined, dried (MgSO₄) and concentrated under reduced pressure. Purification by column chromatography over silica gel (gradient from 5% diethyl ether in light petroleum ether to 20% diethyl ether in light petroleum ether) afforded styrene **12ag** (0.761 g, 71%) as a pale yellow oil; *R*_f (40% diethyl ether in hexane) 0.32; *v*_{max}(film)/cm⁻¹ 1731, 1504, 1428, 1271, 1251, 1215, 1179, 1142, 1103, 984, 941, 889, 847; δ_{H} (400 MHz, CDCl₃) 3.40 (3 H, s, OCH₃), 3.55–3.58 (2 H, m, OCH₂CH₂O), 3.85–3.89 (2 H, m, OCH₂CH₂O), 4.91 (2 H, s, OCH₂O), 7.32 (2 H, br. d, *J* 8.9, Ar*H*), 7.59 (2 H, br. d, *J* 8.9, Ar*H*); δ_{C} (100 MHz, CDCl₃) 58.5, 68.2, 71.0, 95.3 (t, ⁴*J*_{C-F} 3.1), 114.1 (dd, ²*J*_{C-F} 35.1, 19.8), 118.2 (q, ¹*J*_{C-F} 320.1), 121.1, 128.0 (dd, ⁴*J*_{C-F} 6.3, 3.4), 130.3 (br. d, ³*J*_{C-F} 6.3), 148.4, 155.3 (app. t, ¹*J*_{C-F} 291.7); δ_{F} (376 MHz, CDCl₃) -72.8 (3 F, s), -95.6 (1 F, d, ²*J*_{F-F} 51.8), -104.4 (1 F, d, ²*J*_{F-F} 51.8); [HRMS (ES-TOF, [M + Na]⁺) Found: 415.0247; Calc. for C₁₃H₁₃O₆F₅SNa: 415.0251]; *m/z* (CI) 393 (2%, [M + H]⁺), 89 (100), 59 (30); GC (98%) *t*_R 11.87 min (70–320 °C, 20 °C min⁻¹).

Preparation of 12be by interchanging the oxidative addition/transmetallation species

1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 13. A solution of iodine (2.54 g, 10 mmol in 10 cm³ of THF) was added dropwise to alkenylzinc reagent **9b** (40 cm³ of a 0.25 M solution in THF) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 cm³) and extracted with diethyl ether (2 × 40 cm³). The organic extracts were combined, washed with saturated sodium sulfite solution (40 cm³), dried (MgSO₄) and concentrated under reduced pressure to a brown oil. Distillation afforded iodide **13** (2.17 g, 71%) as a pale yellow oil; bp 50 °C/2 mmHg (Kugelrohr); δ_{H} (400 MHz, CDCl₃) 1.19 (6 H, br. t, *J* 6.9, N(CH₂CH₃)₂), 3.25–3.39 (4 H, m, N(CH₂CH₃)₂); δ_{C} (100 MHz, CDCl₃) 13.2, 14.2, 42.0, 42.9, 60.7 (dd, ²*J*_{C-F} 58.2, 27.4), 151.3, 153.8 (dd, ¹*J*_{C-F} 280.0, 297.7); δ_{F} (376 MHz, CDCl₃) -84.9 (1 F, d, ²*J*_{F-F} 42.3), -98.5 (1 F, d, ²*J*_{F-F} 42.3). These data are consistent with those reported by Percy and co-workers.⁴³

1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(2'-methylphenyl)ethene 12be. Iodide **13** (0.153 mg, 0.5 mmol) in dry DMF (3 cm³) was added to a mixture of 2-methylbenzeneboronic acid (75 mg, 0.55 mmol), dichlorobis(triphenylphosphino)palladium(II) (18 mg, 0.025 mmol) and potassium phosphate (160 mg, 0.75 mmol). The mixture was heated at 100 °C for 16 h, then cooled to room temperature. Water (10 cm³) was added and the mixture was extracted with diethyl ether (3 × 30 cm³); the combined organic extracts were washed with brine (10 cm³) then dried (MgSO₄). Purification by column chromatography over silica gel (16% diethyl ether in hexane) afforded styrene **12be** (114 mg, 85%) as a pale yellow oil; *R*_f (15% diethyl ether in hexanes) 0.4; *v*_{max}(film)/cm⁻¹ 1731, 1421, 1385, 1272, 1226, 1150,

987, 752; δ_{H} (300 MHz, CDCl_3) 0.98–1.21 (6 H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.40 (3 H, s, ArCH_3), 3.17–3.39 (4 H, m, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.09–7.41 (4 H, m, ArH); δ_{C} (75 MHz, CDCl_3) 13.3, 14.1, 19.5, 41.9, 42.4, 111.1 (dd, $^2J_{\text{C-F}}$ 46.3, 18.7), 125.7, 129.2, 129.4, 130.1, 130.4, 137.8, 153.0, 154.1 (dd, $^1J_{\text{C-F}}$ 291, 283); δ_{F} (282 MHz, CDCl_3) –97.2 (1 F, d, $^2J_{\text{F-F}}$ 53.7), –106.0 (1 F, d, $^2J_{\text{F-F}}$ 53.7); [HRMS (ES-TOF, $[\text{M} + \text{Na}]^+$) Found: 292.1129; Calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_2\text{F}_2\text{Na}$: 292.1125]; m/z (EI) 269 (18%, M^+), 119 (11), 100 (100), 91 (8) and 72 (35).

Preparation of **12ag** by a ligand-free potassium trifluoroborate coupling protocol

Potassium 2,2-difluoro-1-(2'-methoxy-ethoxymethoxy)ethenyl trifluoroborate 8. *n*-Butyllithium (100 cm^3 of a 2.5 M solution in hexanes, 0.25 mol) was added dropwise to a solution of diisopropylamine (35.27 cm^3 , 0.25 mol) in THF (135 cm^3) at –78 °C. The colourless solution was allowed to warm to –30 °C for 10 min and then re-cooled to –78 °C. Acetal **3a** (22.4 g, 0.12 mol) was added dropwise over 30 min *via* a dropping funnel and the brown reaction mixture was stirred at –78 °C for 2 h. Trimethylborate (42 cm^3 , 0.38 mol) was added in one portion and left to stir and warm to room temperature over 3 h. The now orange reaction solution was cooled to 0 °C and a solution of KHF_2 (117 g in 300 cm^3 of water, 1.5 mol) was added dropwise *via* a dropping funnel. The reaction mixture was stirred at room temperature overnight, then the solvent and water were removed under reduced pressure to reveal a white solid. The crude product was extracted into hot acetone (5 \times 100 cm^3) and hot filtered. Removal of acetone under reduced pressure revealed an orange solid that was recrystallised from acetone; trifluoroborate **8** (17.79 g, 55%) was collected by filtration as fine colourless needles. mp 131–132 °C, δ_{H} (400 MHz, D_2O) 3.26 (3H, s, OCH_3), 3.51–3.55 (2H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.74–3.78 (2H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.79 (2H, s, OCH_2O); δ_{C} (100 MHz, D_2O) 57.6, 67.1, 70.5, 94.7, 159.3 (br. dd, $^1J_{\text{C-F}}$ 296.3, 277.5); δ_{F} (376 MHz, D_2O) –93.3 (1F, d, $^2J_{\text{F-F}}$ 69.0), –110.2 (1F, dq, $^2J_{\text{F-F}}$ 69.0, $^3J_{\text{F-B}}$ 10.8), (–138.7)–(–139.3) (3F, m); m/z (EI) 235 (100%, $[\text{M} - \text{K}]^+$), [HRMS (NSI, $[\text{M} - \text{K}]^+$) Found: 235.0564; Calc. for $\text{C}_6\text{H}_9\text{BF}_5\text{O}_3$: 235.0565]. The data reported by Katz and co-workers did not include C–F coupling constants.³⁶

2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-[4''-(trifluoromethanesulfonyloxy) phenyl] ethene 12ag. Triethylamine (2.0 cm^3 , 14.8 mmol) was added dropwise over 5 min to a mixture of (4-iodophenyl) trifluoromethanesulfonate (1.56 g, 4.44 mmol), borate **8** (1.35 g, 4.93 mmol) and *bis*(dibenzylideneacetone)palladium(0) (142 mg, 0.25 mmol) in *n*-propanol (22.5 cm^3). This mixture was stirred at 90 °C for 21 h, then diluted with Et_2O (50 cm^3) and washed with NaHCO_3 (30 cm^3 of a saturated aqueous solution). The mixture was filtered through Celite then the organic layer was separated, dried (MgSO_4) and the solvent removed was under reduced pressure. The residue was purified by flash column chromatography (10% diethyl ether in light petroleum ether) to afford triflate **12ag** as a yellow oil (1.03 g, 65%, 36% over two steps from **3a**); the data were in agreement with those reported earlier.²⁸

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Notes and references

- 1 E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821.
- 2 A. O. King, N. Okukado and E. I. Negishi, *J. Chem. Soc., Chem. Commun.*, 1977, 683.
- 3 G. Manolikakes, C. M. Hernandez, M. A. Schade, A. Metzger and P. Knochel, *J. Org. Chem.*, 2008, **73**, 8422.
- 4 M. Pour and E. Negishi, *Tetrahedron Lett.*, 1997, **38**, 525.
- 5 E. Negishi, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 233.
- 6 D. T. Hung, J. B. Nerenberg and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 11054.
- 7 A. B. Smith, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. P. Qiu, H. Arimoto, D. R. Jones and K. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8654.
- 8 E. Negishi, A. Alimardanov and C. D. Xu, *Org. Lett.*, 2000, **2**, 65.
- 9 F. Zeng and E. Negishi, *Org. Lett.*, 2001, **3**, 719.
- 10 C. K. Skepper, T. Quach and T. F. Molinski, *J. Am. Chem. Soc.*, 2010, **132**, 10286.
- 11 H. E. Bartrum and R. F. W. Jackson, *Synlett*, 2009, 2257.
- 12 R. F. W. Jackson, I. Rilatt and P. J. Murray, *Org. Biomol. Chem.*, 2004, **2**, 110.
- 13 I. Rilatt, L. Caggiano and R. F. W. Jackson, *Synlett*, 2005, 2701.
- 14 C. Duplais, A. Krasovskiy, A. Wattenberg and B. H. Lipshutz, *Chem. Commun.*, 2010, **46**, 562–564.
- 15 A. Krasovskiy, C. Duplais and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2009, **131**, 15592.
- 16 A. Krasovskiy, C. Duplais and B. H. Lipshutz, *Org. Lett.*, 2010, **12**, 4742.
- 17 M. Mosrin and P. Knochel, *Org. Lett.*, 2009, **11**, 1837.
- 18 T. Bresser and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 1914.
- 19 J.-F. Normant, *J. Organomet. Chem.*, 1990, **400**, 19.
- 20 J. Ichikawa, *J. Fluorine Chem.*, 2000, **105**, 257.
- 21 L. R. Cox, G. A. DeBoos, J. J. Fullbrook, J. M. Percy and N. Spencer, *Tetrahedron: Asymmetry*, 2005, **16**, 347.
- 22 A. Arany, P. J. Crowley, J. Fawcett, M. B. Hursthouse, B. M. Kariuki, M. E. Light, A. C. Moralee, J. M. Percy and V. Salafia, *Org. Biomol. Chem.*, 2004, **2**, 455.
- 23 P. J. Crowley, J. Fawcett, G. A. Griffith, A. C. Moralee, J. M. Percy and V. Salafia, *Org. Biomol. Chem.*, 2005, **3**, 3297.
- 24 G. A. DeBoos, J. J. Fullbrook and J. M. Percy, *Org. Lett.*, 2001, **3**, 2859.
- 25 For aldol reactions of these species, see W. Xu, M. Medebielle, M. H. Bellance and W. R. Dolbier, *Adv. Synth. Catal.*, 2010, **352**, 2787.
- 26 For a review of fluoroketones in medicinal chemistry, see M. Sani, R. Sinisi and F. Viani, *Curr. Top. Med. Chem.*, 2006, **6**, 1545.
- 27 For a recent reaction of the related enolates, see C. H. Han, E. H. Kim and D. A. Colby, *J. Am. Chem. Soc.*, 2011, **133**, 5802.
- 28 J. J. Fullbrook, Ph. D Thesis, *Generating Diversity in α,α -Difluoromethyl Ketones*, University of Birmingham, 2002.
- 29 H. Amii, T. Kobayashi, Y. Hatamoto and K. Uneyama, *Chem. Commun.*, 1999, 1323.
- 30 H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119.
- 31 S. Darses, J. P. Genêt, J. L. Brayer and J. P. Demoute, *Tetrahedron Lett.*, 1997, **38**, 4393.
- 32 S. Darses, G. Michaud and J. P. Genêt, *Tetrahedron Lett.*, 1998, **39**, 5045.
- 33 G. A. Molander and L. A. Felix, *J. Org. Chem.*, 2005, **70**, 3950.
- 34 For a review of the wide ranging applications of these reagents, see G. A. Molander and N. Ellis, *Acc. Chem. Res.*, 2007, **40**, 275.

- 35 T. Siu, J. Young, M. Altman, A. Northrup, M. Katcher, E. Sathyajith, E. Kozina, S. Peterson and M. Childers, *Int. Pat. Appl. Publ.*, (2009) *Inhibitors of Janus Kinases*, Merck & Co Inc., WO 2009/035575 A1.
- 36 J. D. Katz, B. T. Lapointe and C. J. Dinsmore, *J. Org. Chem.*, 2009, **74**, 8866.
- 37 R. Anilkumar and D. J. Burton, *Tetrahedron Lett.*, 2002, **43**, 2731.
- 38 A. Raghavanpillai and D. J. Burton, *J. Org. Chem.*, 2004, **69**, 7083.
- 39 L. Jin, C. Liu, J. Liu, F. Hu, Y. Lan, A. S. Batsanov, J. A. K. Howard, T. B. Marder and A. Lei, *J. Am. Chem. Soc.*, 2009, **131**, 16656.
- 40 E. Hevia, J. Z. Chua, P. Garcia-Alvarez, A. R. Kennedy and M. D. McCall, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **107**, 5294.
- 41 G. T. Achonduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien and M. G. Organ, *Chem. Commun.*, 2010, **46**, 4109.
- 42 S. T. Patel, J. M. Percy and R. D. Wilkes, *Tetrahedron*, 1995, **51**, 9201.
- 43 J. A. Howarth, W. M. Owton, J. M. Percy and M. H. Rock, *Tetrahedron*, 1995, **51**, 10289.
- 44 A 0.5 eq excess of LDA provided 100% conversion while stoichiometric amounts did not. The sensitive difluorinated carbon generated from this reaction tolerates an excess of the non-nucleophilic amido base but undergoes an addition/elimination reaction when an excess of the more nucleophilic *tert*-butyllithium is used.
- 45 E. J. Corey, J. L. Gras and P. Ulrich, *Tetrahedron Lett.*, 1976, **17**, 809.
- 46 M. Isobe, S. Kondo, N. Nagasawa and T. Goto, *Chem. Lett.*, 1977, **6**, 679.
- 47 M. P. Sibi and V. Snieckus, *J. Org. Chem.*, 1983, **48**, 1935.
- 48 For a review of the DoM heirarchy and CIP effect, see M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206 and references therein.
- 49 T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385.
- 50 D. Seebach, *Chem. Br.*, 1985, **21**, 632.
- 51 D. Seebach, A. Thaler and A. K. Beck, *Helv. Chim. Acta*, 1989, **72**, 857.
- 52 B. M. Coleridge, C. S. Bello, D. H. Ellenberger and A. Leitner, *Tetrahedron Lett.*, 2010, **51**, 357.
- 53 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.
- 54 We are considering a standard mechanism for couplings of this type in which transmetalation and reductive elimination are usually the key events: see ref. 39.
- 55 G. A. DeBoos, J. J. Fullbrook, W. M. Owton, J. M. Percy and A. C. Thomas, *Synlett*, 2000, 963.
- 56 For related Suzuki couplings, see A. Raghavanpillai and D. J. Burton, *J. Org. Chem.*, 2006, **71**, 194.
- 57 1-Iodo-4-nitrobenzene was used instead of bromide as it was available in our laboratory.
- 58 Katz and co-workers also identified HF addition products, including **14**, when generating styrenes bearing a strong EWG in the *para* position.
- 59 *Spartan '08, Wavefunction*, Irvine CA 2008.
- 60 *Gaussian '09, Revision A.1*, M. J. Frisch *et al.*, Gaussian, Inc., Wallingford CT, 2009. The full reference is given in the supplementary information†.
- 61 Lei's gas and solution data run closely parallel. The THF and gas phase data differ by an approximately fixed amount so no additional insight accrues about the differences between organozinc species.
- 62 For recent structural and kinetic work probing structure/reactivity relationships in alkylzinc chemistry, see (a) I. Rilatt and R. F. W. Jackson, *J. Org. Chem.*, 2008, **73**, 8694; (b) F. Dreiocker, J. Oomens, A. Meijer, B. T. Pickup, R. F. W. Jackson and M. Schafer, *J. Org. Chem.*, 2010, **75**, 1203; (c) A. J. Ross, F. Dreiocker, M. Schafer, J. Oomens, A. Meijer, B. T. Pickup and R. F. W. Jackson, *J. Org. Chem.*, 2011, **76**, 1727.
- 63 L. Caggiano, R. F. W. Jackson, A. Meijer, B. T. Pickup and K. A. Wilkinson, *Chem.–Eur. J.*, 2008, **14**, 8798.
- 64 Persson and co-workers have detected a dominant pentacoordinate geometry for Zn²⁺ in DMPU solution; in the solid state, tetra-coordinate species obtain. See D. Lundberg, L. Eriksson, P. D'Angelo and I. Persson, *J. Mol. Liq.*, 2007, **131–132**, 105.
- 65 For a recent study evolving Hammett relationships for Negishi coupling, see Z. B. Dong, G. Manolikakes, L. Shi, P. Knochel and H. Mayr, *Chem.–Eur. J.*, 2010, **16**, 248.
- 66 For recent detailed investigations of aspects of Negishi coupling chemistry, see (a) J. A. Casares, P. Espinet, B. Fuentes and G. Salas, *J. Am. Chem. Soc.*, 2007, **129**, 3508; (b) B. Fuentes, M. Garcia-Melchor, A. Lledos, F. Maseras, J. A. Casares, G. Ujaque and P. Espinet, *Chem.–Eur. J.*, 2010, **16**, 8596; (c) G. A. Chass, C. J. O'Brien, N. Hadei, E. A. B. Kantchev, W. H. Mu, D. C. Fang, A. C. Hopkinson, I. G. Csizmadia and M. G. Organ, *Chem.–Eur. J.*, 2009, **15**, 4281.
- 67 Note added in proof: these distances and angles were measured from the B3LYP/SDD(6-31G*) structures.